Title: Toxicity of Radiosurgery for Brainstem Metastases

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Keywords

Brainstem; metastasis; stereotactic radiosurgery; toxicity

Running Title: Toxicity rates after SRS for brainstem metastases

Funding- None

Conflict of Interest- None

Abstract

Although stereotactic radiosurgery (SRS) is an effective modality in the treatment of brainstem metastases (BSM), radiation induced toxicity remains a critical concern. To better understand how severe or life-threatening toxicity is affected by the location of lesions treated in the brainstem, a review of all available studies reporting SRS treatment for BSM was performed. Twenty-nine retrospective studies investigating SRS to BSM were reviewed. The rates of grade 3 or greater toxicity, based on the Common Terminology Criteria for Adverse Events varied from 0-9.5% (mean 3.4% ± 2.9%). Overall, the median time to toxicity after SRS was 3 months, with 90% of toxicities occurring before 9 months. A total of 1243 cases had toxicity and location data available. Toxicity rates for lesions located in the medulla were 0.8% (1/131), compared to midbrain and pons respectively, 2.8% (8/288) and 3.0% (24/811). Current data suggests that brainstem substructure location does not predict for toxicity and lesion volume within this cohort with median tumor volumes 0.04-2.8 cc does not predict for toxicity.

Introduction

Stereotactic radiosurgery (SRS) for brainstem metastases (BSM) has been shown to be a safe and effective modality [1-31]. Reported rates of local tumor control in patients who received SRS for BSM vary from 74-100% and the median survival ranges from 4-12 months [1-28,30-32]. Despite the promising results of SRS with respect to local control and survival, toxicity due to radiation is always a concern, with severe to life threatening toxicities being reported in 0-9.5% of patients with BSM treated with SRS [2-10,12-14,16-18,20-28,30-32]. Majority of papers have not analyzed the impact of location on toxicity or volume of lesions on toxicity [2-10,12-14,16-18,20-28,30-32]. Due to a relatively small sample size, the preferred dose to treat BSM remains controversial with literature varying on the dosing strategies [2-10,12-14,16-18,20-28,30-32]. This review paper aims to synthesize the collective literature available on SRS to BSM.

Methods

In order to identify brainstem location specific toxicity after SRS "Brainstem metastases radiosurgery," was searched as a keyword in PubMed and Ovid (MEDLINE). Primary literature specific to treatment of BSM with SRS was reviewed. Only retrospective studies of patients treated with SRS for BSM were available; (shown in *Figure 1).* This literature review does not include brainstem metastases that are described in larger non-brainstem studies. Some authors were contacted for the details regarding the reported toxicities [2,15,30] Of the two Trifiletti papers including the institutional and international papers, only the data from the institutional paper, which provided the pertinent information, was used for the location based toxicity analysis in order to avoid duplicate inclusion of cases [22,23]. All the remainder of papers were included with no obvious concern for duplication in reported cases. For one report that did not specify the number of lesions per patient, the number of lesions were assumed to be equal to the number of patients for the purposes of this review (n=41) [18].

The following data were collected from each manuscript: method of SRS, total number of patients, total number of lesions, locations of lesions, median or mean age, median or mean Karnofsky Performance Status (KPS), median or mean prescription dose (most reports included only margin dose information and prescription isodose information was often not available), number of patients who received whole brain radiation therapy (WBRT), mean or median survival after SRS, local tumor control rate, radiation induced toxicity, and mean or median tumor volume. The mean rate of local control, toxicity, and WBRT were calculated based on values in all reports.

For this analysis, only toxicities of grade 3 or greater were included in this review [33]. Not all reports explicitly stated whether the toxicity was grade 3 or greater based on the Common Terminology Criteria for Adverse Events, but it was inferred based on the description of toxicity and treatment if it could be classified as grade 3 or greater. For example, if a manuscript described a case of toxicity where radionecrosis was refractory to steroids than this was counted as a toxicity ≥ grade 3. The details of the grading of toxicity are presented in Table 1. Grade 2 toxicity could not be reviewed because there was no specification on exactly how many patients developed grade 2 toxicities in manuscripts. There were two Trifiletti paper that could have obscured the data, care was taken to avoid this. In one instance, the institutional data was removed to tabulate the occurrence of metastases in the substructures and in the other instance the international paper by Trifiletti et al. was removed because it did not report both location and toxicity. This was clarified by the authors of the paper as well.

The following variables were included when tabulating the toxicities, to the extent available: gender, age, primary cancer histology, location of treated lesion, volume of tumor, dosage of SRS, whether WBRT was given or not, the type of toxicity, time to toxicity from SRS

treatment, and status of local control. An unpaired t-test was used to compare the means of the volumes of the lesions with toxicity and those without toxicity.

Results

The searches identified twenty-nine retrospective studies of BSM treated with SRS published from 1999-2017. The details of these reports are summarized in Table 2, listed chronologically and by first author. SRS modalities reported include Gamma Knife (GK), LINAC (Linear Accelerator), and Cyber Knife (CK). A total of 2037 SRS treated metastases were reported in 1878 patients. The median age ranged from 50-69 years old and the mean age ranged from 52.9-64 years old. The median KPS ranged from 70-90.

1) Summary of Literature

Out of 29 reports 26 specified the locations of the lesions. One report did not account for the location of 8 out of 52 lesions and two other reports did not comment on the location of BSM [9,10,18]. This resulted in a total of 1945 lesions with the location of the BSM specified; the most common location was the pons, representing 62.8% (1222/1945) of the cases; the midbrain was the next most common, representing 22.4% (436/1945) of cases; and 9.6% (186/1945) of cases were found in the medulla. Other structures represented 5.2% of cases; the pontomesencephalic junction accounted for 2.7% (52/1945) of cases, the pontomedullary junction accounted for 1.4% (27/1945) of cases and the cerebellopontine angle (CPA) that extended into brainstem proper accounted for 1.2% (24/1945) of cases. Removing the institutional report by Trifiletti, to avoid accounting for some patients twice, resulted in 22.8% (400/1756) of cases in the midbrain, 62.2% (1093/1756) in the pons, 9.8% (172/1756) in the medulla, and the other 5.2% in junctions among the substructures of the brainstem [23].

The radiosurgery characteristics were as follows. The median prescription dose ranged between 13-18 Gy. WBRT prior to or after SRS ranged from 6.5% - 96.4% with the mean being 48.4±19.8%. The local control rate at 12 months varied from 74-100%. The median overall survival ranged from 3.9-17.2 months. The local control rate at 12 months based on the mean of all the reported values in literature turned out to be 86.7% ± 5.9%, all but one manuscript reported local control rates at 12 months [12]. Removing the institutional Trifiletti study resulted in less than 1% variation in the mean of the local control rate [23]. The median tumor volume ranged from 0.04-2.8 cc and the mean tumor volume ranged from 0.7-2.8 cc.

2) Toxicity

A total of 2037 cases were reviewed; 58 were excluded for lack of comments on toxicity [1,19]. A total of 79 patients were reported in the literature to have suffered from toxicity out of 1979 potential cases. Rate of toxicity reported in patients treated with SRS for BSM varied from 0-9.5%. The average rate of toxicity based on reported percentages per report was 3.4% ± 2.9%.

To analyze location based toxicity 1979 cases reviewed, 84 were excluded because there was no comment on location [10,18] and 644 were excluded for lack of location associated with toxicity [17,22]. This resulted in 1251 cases that commented on both location and toxicity. It is imperative to note that this exclusion accounted for any potential overlap between the Trifiletti studies and only the institutional one was used for the location-based toxicity analysis [22,23]. In the studies which contained locations of toxicities, 23.0% (288/1251) of all treated BSM were in the midbrain, 64.8% (811/1251) in the pons, and 10.5% (131/1251) in the medulla. An additional eight lesions did not account for the location in one report and the other 1% of lesions were either in the CPA or midbrain pons junction [9]. The rates of grade 3 or greater toxicity associated

with treatments to metastases in the midbrain, pons, and medulla were 2.8% (8/288), 3.0% (24/811), and 0.8% (1/131) respectively.

To compare treatment and tumor characteristics amongst the substructures, seven reports were examined that commented on both toxicity and location, with patient level data available for 260 cases (of 1251 possible) [6,15-17,21,28,31]. One report was missing tumor volume data for 3 lesions [6]. A total of 30 patients had metastases that were treated in the medulla. The median volume was 0.5 cc (mean 1.1 cc, range 0.01-12.2 cc). The median prescription dose was 16 Gy (mean 16.8 Gy, range 10-24 Gy). In the midbrain, 56 cases were reported with 16 Gy as the median prescription dose (mean 16.7 Gy, range 8-24 Gy) and 0.3 cc as the median volume (mean 0.8 cc, range 0.01-6.1 cc). In the pons, 174 cases were available with a median prescription dose of 16 Gy (mean 16.3 Gy, range 8-24 Gy) and a median volume of 0.3 cc (mean 1.2 cc, range 0.004-12 cc), suggesting that treatments and lesions were similar among the brainstem substructures in the subset of patients with available data.

To compare the volumes of the lesions with and without toxicity the same seven reports from the previous paragraph were used. This resulted in 260 possible patients that could be analyzed based on patient level data available and development of toxicity [6,15-17,21,28,31]. For the lesions that developed toxicity (n=10) this resulted in a mean volume of 1.6 ± 1.0 cc. For the rest of the patients in the reports (n-247) the mean volume was 1.1 ± 1.2 cc. The two-tailed P value equals 0.2 for the comparison of these two means.

The reported 79 cases with toxicity were reviewed to summarize patient and treatment factors potentially associated with toxicity. Only 35 of the 79 toxicity cases reported in the literature were described in more detail [2,4,6-9,13,14,17,18,21,23,25,27,28,30]. The details of the 35 cases are summarized in Table 3. In this toxicity cohort, 22.8% of cases were in the midbrain, 68.6% in the

pons, 2.9% in the medulla, and 5.7% did not have a location reported. All reported toxicities occurred before 18 months and with a median time to toxicity of 3.0 months. The median prescription dose was 15 Gy for midbrain cases and 16.3 Gy for pons cases. Midbrain BSM had a median volume of 0.9 cc (range: 0.1-3.3 cc) and pons cases a median volume of 1.3 cc (range: 0.1-5.8 cc).

Discussion

Radiosurgery has consistently been proven to be a safe and effective treatment for BSM, yet toxicity remains a concern for both the patient and physician[1-28,30,32]. The last review article that addressed clinical outcomes after SRS for BSM was published in 2013 and synthesized 12 reports [11]. Based on limited number of cases in previously published reports about BSM, it has been difficult to synthesize data and comment on the treatment preferences for BSM and other characteristics that influence toxicity rates. Thus, a review of the available literature was performed to comment on the varying doses used in the literature and analyze the rate of radiation induced toxicities with respect to different locations in the brainstem and volume. Table 2 shows that the most common site of BSM is unequivocally the pons. The median prescription dose varied from 13-18 Gy. The mean local control rate was 86.7 ± 5.9% with the rate of toxicity being 3.4 ± 2.9%.

Interestingly, the median time to development of toxicity from SRS to BSM was 3 months with greater than 90% occurrence before 9 months. In contrast, lesions in the cerebral parenchyma exhibited median time to toxicity at 4.5 months (range 0.5-36.0 months) in randomized controlled trials (RCT) [34]. In another RCT evaluating the combination of SRS and WBRT for brain metastases in which 9% of the patients developed toxicity; a third of the 9% developed toxicity before 3 months and the other two-thirds after 3 months[35]. Reasons for the

accelerated onset of toxicity associated with brainstem lesions remain to be determined but may be due to lack of compressibility in the surrounding space for edema when compared to the cerebral hemispheres.

Consistent with previous reports suggesting that both melanoma and RCC are known to spontaneously result in intracranial hemorrhages [36,37], 4 of the 6 melanoma BSM toxicities and 1 of the 3 renal cell carcinoma (RCC) toxicities were hemorrhages. Based on the above results of the 35 toxicities summarized in Table 3, development of toxicity occurs at a variety of prescription doses of SRS. The median prescription dose of cases with reported toxicity was 16 Gy and two-thirds of the cases were accounted for by a prescription dose up to 18 Gy. It has previously been reported that higher doses lead to more toxicity but based on the data in Table 3 it seems toxicity can occur at a wide range of doses [22]. Patient level data on tumor volume or radiation dose was not available in all toxicity cases for this analysis. Thus, the impact of tumor volume and radiation dose on toxicity could not be analyzed on a larger scale in a location specific manner.

Interestingly, only one toxicity in the medulla was reported. A large study reporting 44 grade 3 and higher toxicities concluded that location did not predict toxicity [22]. Location specific toxicity data was not available in this report and thus was not incorporated into the location analysis. Location specific treatment volumes and radiation dose are reported only on a small subset of patients and thus there is a possibility that treatment preferences and lesion characteristics based on location differ [6,16,21,28]. Six case reports were excluded from the review that involved BSM treated via SRS, but none of the lesions in those reports were in the medulla [38-43]. The higher prevalence of toxicity in pontine lesions is likely associated with the frequency of occurrence of BSM in the pons.

There are several limitations to this report. Given the design of this study, it is inherently limited by the quality of the reports included. For instance, the prescription dose was commonly reported as the 'marginal dose' with no reference of the isodose line to which the prescription dose was defined in the majority of the studies. Sadly, in retrospective studies planning details such as rapid dosage drop to the surrounding parenchyma are not easily reported and this could lead to variation in the data. It should be noted that not all studies detail treatment or lesion characteristics of brainstem metastasis. It is also uncertain if the reports that do include specific details are representative of the broader series. This data also might not be representative of the percentage of patient the develop toxicity after SRS to BSM, since many patients might not survive long enough for toxicities to develop. Further investigations might provide more insight into treatment preferences and why/if medulla toxicities are truly rare.

Conclusion

In conclusion, for BSM treated via SRS, the median prescription doses vary from 13-18 Gy, with a local control rate of 86.7 ± 5.9% and a rate of toxicity of 3.4 ± 2.9%. The most common site of BSM is the pons. The median time to toxicity is 3 months for BSM treated by SRS. The current literature reports that some BSM may be safely treated with a prescription dose of up to 18 Gy or more and that volume and location do not predict for toxicity. More research is needed to further clarify these trends. This data shows that no recipe for safe treatment of brainstem metastases does (yet) exist, but in most cases local tumor control can be achieved with acceptable toxicity.

Funding- None

Acknowledgements- Patti Raley, MS, ELS for help with editing the manuscript.

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Figure Legend

Figure 1: Flow Diagram

***Table 1**: Relevant nervous system specific toxicity grading for adverse events from NIH NCI CTCAE.*

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.
Edema	-	-	-	Life-threatening consequences; urgent intervention indicated.	
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Table 2: *Summary of BSM treated by SRS studies.*

Author	Year	Method	Pts/Lesions	Location Mb/(MP)/Po/(PM)/Mu/(CP)	Median Age (years)	Median KPS	Median Margin Dose (Gy)	No of pts w/ WBRT	Median Survival (months)	Local Tumor Control Rate (%)	Toxicity (%)	Median Tumor Volume (cc)
Huang	1999	GK	26/27	6/21/0	56[a]	80[a]	16	24/92% [c]	9	95	0	1.1
Shuto	2003	GK	25/31	10/19/2	57.1[a]	NR	13[a]	7/28%[c]	49	77.4	8	2.1[a]
Fuentes	2006	GK	28/28	9/17/2	57.7[a]	80[a]	19.6[a]	6/21%[c]	12	92	NR	2.1[a]
Yen	2006	GK	53/53	8/42/3	57.3[a]	80	18	21/40%	11	86.5	0	2.8[a]
Hussain	2007	GK	22/25	9/12/4	60	90	16	3/14% (after)	8.5	100	4.5	0.9
Kased	2008	GK	42/44	7/31/6	55	90	16	24/57%[c]	9	77	9.5	0.3
Lorenzoni	2009	GK	25/27	9/14/4	54[a]	90	20[a]	17/68%[c]	11.1	95	0	0.6[a]
Samblas	2009	LINAC	28/30	8/20/2	52.9[a]	NR	11.1[a]	27/96.4% [c]	16.8[a]	96.4	NR	1.9[a]
Koyfman	2010	GK	43/43	NR	59	80	15	34/79%[c]	5.8	85	0	0.4

Valery	2011	LINAC	30/30	9/16/5	57	80[a]	13.4	8/27%	10	79	0	2.8
Kelly	2011	LINAC	24/24	10/13/1	57	80	13	23/96%	5.3	78.6	8.3	0.2
Yoo	2011	GK	32/32	6/23/3	56.1[a]	NR	15.9	NR	7.7[a]	87.5	3.1	1.5[a]
Hatiboglu	2011	LINAC	60/60	15/39/6	61	90	15	15/25%[c]	4	76	3.3	1
Lin	2012	LINAC	45/48	7/35/6	59.9[a]	80	14	21/44%	11.6	88	4.7	0.4
Leeman	2012	LINAC	36/38	11/25/2	62	80	17	18/47%	3	93[e]	0	0.9
Li	2012	GK	28/32	8/21/3	61	80	16	0/0%	9	90.6	3.6	0.8
Kawabe	2012	GK	200/222	65/121/36	64[a]	90	18	13/6.5%	6	81.8	0.5	0.2
Sengoz	2013	GK	44/46	14/30/2	57	80	16	29/66%[c]	8	96	0	0.6
Jung	2013	GK	32/32	9/18/5	50	NR	13	19/59%[c]	5.2	87.5	0	0.7
Peterson	2014	GK	41/?	NR	59	NR	17[a]	19/46%	4.4	91	2.4	0.7[a]

Kilburn	2014	GK	44/52	9/(3)/28/4[b]	57	80	18	25/57%	6	74	9.1	0.1
Voong	2015	GK	74/77	11/60/6	59	90	16	43/58%[c]	3.9	94	8	0.1
Liu	2015	CK	54/66	12/49/5	59	70	17.9[f]	34/51.5%[d]	5	80	1.5	0.1
Trifiletti	2015	GK	161/189	36/129/14/(10)	60.5	80	18	83/51.6%	5.5	87.3	1.8	0.4
Joshi	2016	GK	48/51	10/34/7	62	90	15	19/40%	7.6	89	4	0.1
Trifiletti Int	2016	GK	547/596	126/(44)/345/(22)/45/(14)	61	90	16	266/49%	5.5	81.8	7.4	0.8
Murray	2016	GK	44/48	5/(3)/29/(5)/6	58	NR	15	33/75%[c]	5.4	76.9	8.3	1.3
Nakamura	2017	CK	20/26	4/18/4	69	90	16.4[f]	5/19%[g]	11.5	90	5	0.33
Patel	2018	GK	14/19	3/13/3	56	85	17.5	6/42.8%[c]	17.2	87.5	0	0.04
Total			1878/2037	436/(50)/1222/(27)/186/(24)				48.4±19.8%		86.7±5.9	3.4 ± 2.9	

Abbreviations: CK= Cyber Knife; CP= cerebellopontine angle; GK= Gamma Knife; LINAC= Linear Accelerator; Mb= Midbrain; MP= Pontomesencephalic junction, Mu= Medulla; NR= Not reported; Po= Pons, PM= pontomedullary junction

[a] The mean value is reported instead of the median.

[b] Location of other 8 lesions not specified in report

[c] Patients received WBRT either before or after with no specification in manuscript or it was unclear whether patients received WBRT before or after.

[d] The number of lesions that received WBRT were reported, not number of patients.

[e] This is the local tumor control rate at 6 months, the others are reported at 12 months.

[f] Single Session Equivalent Dose

[g]Lesions receiving WBRT not patients

Table 3: Characteristics of the 35 detailed reports of toxicity in the literature. Note the number in parentheses after the characteristic is the number out of 35 that reported that specific detail.

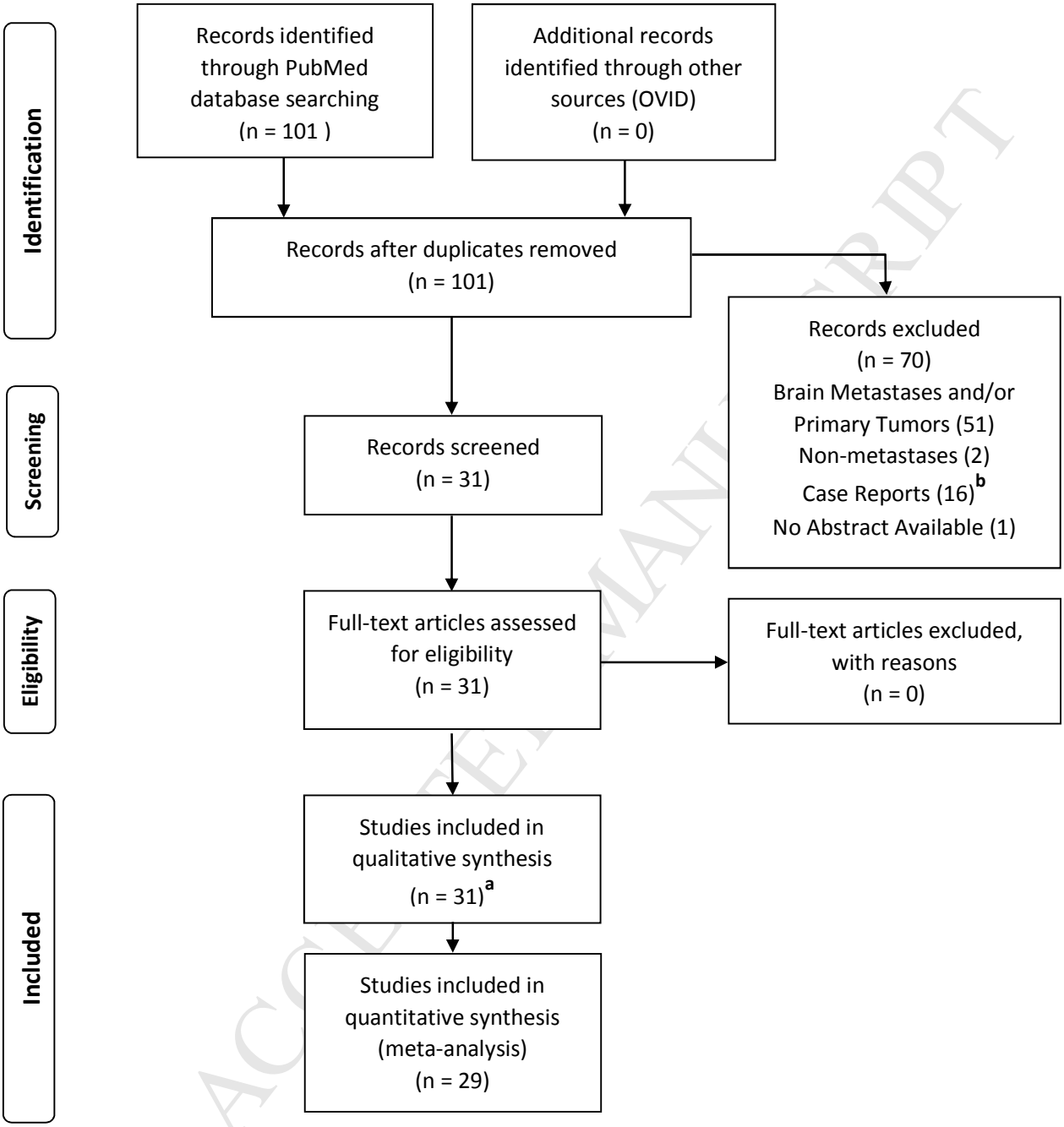
TOTAL 35 CASES	RANGE	MEDIAN/PERCENTAGE
AGE (17) (YEARS)	30-73	59
	30-50	17.6%
	50-60	41.2%
	>60	41.2%
GENDER (22) (M/F)	13/9	59%/41%
HISTOLOGY (29)		
	NSCLC	24.1%
	SCLC	3.4%
	Breast	13.8%
	Melanoma	24.1%
	RCC	10.3%
	Thyroid	3.4%
	Sarcoma	3.4%
	Colon	3.4%
	Ovarian	3.4%
	Unknown	10.3%
LOCATION (34)		
	Midbrain	23.5%
	Pons	73.5%
	Medulla	2.9%
TUMOR VOLUME (29) (CC)	0.1-5.8	1.4cc
	0-1cc	41.4%
	1-2cc	34.5%
	>2cc	24.1%
MARGIN DOSE (31) (GY)	12 to 20	16
	12 -15.9	35.5%
	16-17.9	22.6%
	≥18	41.9%
WBRT (15)		
	Yes	33.3%
	No	66.7%
TOXICITY (27)		
	Hemorrhage	29.6%
	Radionecrosis	29.6%
	Edema	25.9%
	Edema and RN	7.4%
	RN and Hmg	3.7%
	Unkown[a]	3.7%
TIME TO TOXICITY FROM	0-18 months	3 months

SRS (30) (MOS)		
	≤3 months	60.0%
	≤6 months	83.3%
	≤9 months	93.3%
	≤18 months	100%
LOCAL FAILURE (16)		
	Yes	18.8%
	No	81.2%
DOSE BY LOCATION (31)		
MIDBRAIN (6)	15 Gy	
	12-15.9 Gy	50.0%
	16-17.9 Gy	16.7%
	≥18 Gy	33.3%
PONS (24)	16.3 Gy	
	12-15.9 Gy	25.0%
	16-17.9 Gy	29.2%
	≥18 Gy	45.8%
MEDULLA (1)		
	15 Gy	100%
TUMOR VOLUME BY LOCATION (29)		
MIDBRAIN (6)	0.9 cc	
	0-1cc	50%
	1-2cc	33.3%
	>2cc	16.7%
PONS (22)	1.3 cc	
	0-1cc	40.9%
	1-2cc	31.8%
	>2cc	27.3%
MEDULLA (1)		
	1.3cc	100%

Abbreviations: Hmg=Hemorrhage; NSCLC= Non-small cell lung cancer; RCC= Renal cell carcinoma; RN=Radionecrosis; SCLC= Small cell lung cancer

[a] Unknown due to no imaging.

Figure 1: Flow Diagram



[a]Two reports were discounted in the quantitative synthesis because one was a review paper and the other was a matched cohort analysis that included the same cohort of patients as another report already included in the quantitative synthesis.

[b]Most of the case reports were not BSM, only 6 out of the 16 were BSM treated by SRS.

- For BSM treated via SRS, the median prescription doses vary from 13-18 Gy
- For BSM treated via SRS the local control rate is 86.7 ± 5.9%
- For BSM treated via SRS the rate of grade 3 or greater toxicity is 3.4 ± 2.9%.
- The most common site of BSM is the pons.
- The median time to toxicity is 3 months for BSM treated by SRS.
- Volume and location do not predict for toxicity for BSM treated via SRS.

BSM – Brainstem Metastases

SRS – Stereotactic Radiosurgery

KPS – Karnofsky Performance Status

WBRT – Whole Brain Radiation Therapy

GK – Gamma Knife

CK – Cyber Knife

LINAC – Linear Accelerator

CPA – Cerebellopontine Angle

Gy – Gray

NIH – National Institute of Health

NCI – National Cancer Institute

CTCAE – Common Terminology Criteria for Adverse Events

Hmg - Hemorrhage

NSCLC - Non-small cell lung cancer

RCC - Renal cell carcinoma

RN - Radionecrosis

SCLC - Small cell lung cancer

All authors listed in this manuscript have no conflicts of interest to disclose.